A comparison of multidrug-resistant tuberculosis patient costs under molecular diagnostic algorithms in South Africa.

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Conflicts of interest:

The authors declare that there are no conflicts of interest

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SUMMARY

Setting: The study took place in Cape Town, South Africa from 2010-2013 as part of an observational cohort in 10 primary health facilities.

Study Aim: A comparison of costs incurred by patients in MDRTBPlus line probe assay and Xpert MTB/RIF-based diagnostic algorithms, from the onset of illness until multidrug-resistant tuberculosis treatment initiation.

Methods: Eligible patients were identified from laboratory and facility records, interviewed 3-6 months after treatment initiation and a cost questionnaire completed. Direct and indirect costs, individual and household income, loss of individual income and change in household income were recorded in local currency, adjusted to 2013 costs and converted to US$.

Results: The median number of visits to initiation of multidrug-resistant tuberculosis treatment was reduced from 20 to 7 ($p<0.001$) and median costs from $68.1 to $38.3 ($p=0.004$) in the Xpert group. From the onset of symptoms to being interviewed, the proportion unemployed increased from 39% to 73% in the LPA group ($p<0.001$) and from 53% to 89% in the Xpert group ($p<0.001$). There was a decrease of 16% in median household income in the LPA group and 13% in the Xpert group.

Conclusion: The introduction of an Xpert-based algorithm brought relief by decreasing the cost incurred by patients, but the loss of employment and income persist. Patients require support to mitigate this impact.

Key words: molecular diagnostic tests, patient costs, income loss, impact assessment.

BACKGROUND

"TB is the child of poverty - and also its parent and provider" [Archbishop Desmond Tutu.]

Tuberculosis (TB) disproportionately affects the poor(1) due to a complex interaction between many factors, including, poor nutrition, overcrowded living or working conditions, and concomitant disease, such as human immunodeficiency virus (HIV) infection(2,3). TB perpetuates a cycle of poverty with affected families losing household income through disability or death and confronting costs in diagnosing and treating the disease. TB also affects the most economically viable, being among the top three causes of death for women aged 15 - 44 years(4).

TB patients incur significant costs from the onset of their illness until diagnosis, with costs, as a percentage of household income, being higher for poor patients(5–9). Long delays exist between the onset of TB symptoms and initiation of TB treatment, attributed to both the patient and the health system(10,11). The longer this delay, the more likely a patient is to both transmit TB(12) and to incur costs for transport, accessing healthcare, purchasing pharmaceuticals, and losing work time and productivity.

Several systematic reviews report on diagnostic and treatment costs faced by TB patients. Costs ranged widely between countries with one review reporting the largest costs being incurred for hospitalization, medication, transportation and private healthcare(6). Ukwaja et al(13) report mean diagnostic costs for patients in Africa ranging between 10.4% to 35% of mean annual income and concluded that average diagnostic costs for TB were "catastrophic", defined in different studies as costs greater than 10% of monthly or annual household income, greater than 40% of non-subsistence household income, or the use of non-reversible coping strategies (5,14). Patients in the lowest income bracket face the greatest risk of "catastrophic" costs(5). Tanimura et al(14) found that direct medical costs accounted on average for 20%, direct non-medical costs for 20% and income loss for 60% of total cost for patients in low- and middle-income countries. Pre-treatment costs accounted for half of total costs. In Burkina Faso, 72% of patients were found to have incurred direct medical costs during the pre-diagnostic phase(15).

Those with multi-drug resistant (MDR) TB face an even greater economic burden, with low cure rates and lengthy treatment of up to two years(16–18). Three studies reported by Tanimura et al disaggregated the total costs for TB and MDR-TB patients and showed that costs were higher

for those with MDR-TB(14). In one of these studies pre-diagnostic costs for MDR-TB patients were just over double that of TB patients(17). No studies from sub-Saharan Africa were found pertaining specifically to MDR-TB patient diagnostic costs.

Implementation of Xpert MTB/RIF (Xpert) has reduced the time taken to diagnose MDR-TB(19) and it is anticipated that patients will benefit economically through fewer pre-treatment healthcare visits, and the potential for an earlier diagnosis to decrease morbidity and mortality. It is important to ascertain the benefit which new technology affords to vulnerable groups(20). This study compared costs incurred by patients in MDRTBPlus line probe assay (LPA) and Xpert-based diagnostic algorithms, from the onset of symptoms until MDR-TB treatment initiation.

METHODS

Setting:

The study took place in a routine operational setting in Cape Town, South Africa. The country has high levels of poverty, with 56.8% of people living below the poverty line(21). Household incomes show persistent disparities along racial lines, with average annual household income of ZAR387,011 amongst "white" households compared to ZAR 69,632 amongst "black" households and 48.7% of "black" households with annual household income <ZAR9,886(22). The government has implemented a range of social protection measures to combat this, including both conditional (child support and disability grants) and unconditional (pensions for men >65 and women >60-years old) cash transfers and the provision of free primary health services (23).

Free TB diagnostic services were provided at 142 primary health-care (PHC) facilities in Cape Town; 101 of these together with the dedicated TB–hospital offered free TB treatment. There was a PHC facility within about a 5 km radius of all households. TB tests were done at a central laboratory and results recorded in an electronic laboratory database.

In 2010, a smear, culture and LPA-based diagnostic algorithm was in place (Figure 1) with LPA performed on culture isolates in high MDR-risk TB presumptive cases. From 2011 Xpert was sequentially introduced into facilities, replacing smear microscopy for all presumptive TB cases (Figure 1). In both algorithms, cases with a failing 1st line TB treatment regimen were evaluated

for MDR-TB through culture and LPA. We refer to patients diagnosed under these algorithms as the LPA and Xpert groups respectively.

MDR-TB patients received standardised treatment regimens. At the start of data collection in 2010, doctors at the TB hospital reviewed case records and prescribed treatment but most patients initiated treatment at PHC facilities. Since 2012 (mid-way through the study), doctors could initiate MDR-TB treatment at PHC facilities without the need for prior review of case records at the TB-hospital.

Study Population:

The study was part of an observational cohort in 10 high TB-burden PHC facilities selected from a total of 29 that met the criteria of a TB caseload of >350 in 2009. We sorted facilities from best to worst performing based on new smear positive treatment outcomes and randomly selected five facilities above and five below the median treatment success rate of 78%.

Eligible patients diagnosed in either algorithm were >18-years of age, had been diagnosed with rifampicin or rifampicin and isoniazid resistance from sputa tested in Cape Town between June 2010 and December 2012, and had received MDR-TB treatment at one of the 10 PHC facilities. Patients with previous MDR-TB treatment were excluded, as their pathway to care may have been different. Those with pre- or extensively drug-resistant TB or who had interrupted MDR-TB treatment at the time of the scheduled interview were excluded. For infection control and safety of the researchers, only patients who had been on MDR-TB treatment for at least 3 months and were smear negative were interviewed.

Data Sources and Collection:

Patients diagnosed at selected facilities were identified from the electronic laboratory database; those diagnosed elsewhere, but on treatment at selected facilities, were identified from facility DR-TB paper registers and clinical records.

Trained professional nurses located patient folders, reviewed study eligibility and recorded demographic, laboratory and clinical data, and the patients' healthcare visits on case report

forms. The clinical coordinator used this information to populate a timeline on a patient cost questionnaire with the number and dates of visits. This was used to probe and clarify responses provided by the patient during the interview.

Three to six months after the start of treatment, one of two graduate social scientists obtained informed consent and conducted interviews with patients at the PHC facility, in their language of choice. A structured cost questionnaire was completed detailing the patient's care-seeking visits from the reported onset of symptoms to MDR-TB treatment initiation. This included time spent at healthcare facilities, travel time and out of pocket payments. Employment status and individual and household income were assessed both prior to the onset of symptoms and at the time of the interview. The clinical coordinator checked the questionnaire and the text relating to care seeking visits and transcribed data onto a coded spreadsheet.

Costs Assessed:

Direct costs comprised medical (for private practitioner consultation, diagnostic tests and medication) and non-medical (travel for return trips to the healthcare provider) expenditure as reported by patients. Money spent on food and expenditure incurred for persons accompanying the patient were not assessed. Indirect costs comprised opportunity costs for patient time. The number of healthcare visits was determined from the folder review and patient interview. Patient time comprised time spent in a healthcare facility, 8 hours per day for hospitalized patients, and time spent in travel to the healthcare facility. The cost per hour for patient time was calculated for all patients using the hourly wage (ZAR11.17) of a municipal worker in Cape Town in 2013(24). We decided to use a basic wage for all patients as it was difficult to calculate an average hourly wage for the large percentage that were unemployed or self-employed and worked variable hours. The implications of this method are addressed in the discussion.

The total cost to the patient was calculated as the sum of direct and indirect costs. All costs were calculated in local currency (ZAR) for that year, adjusted to 2013 costs using the annual consumer price index(25) and converted to US$ based on average United Nations treasury operational rates in 2013(26).

Definitions:

Healthcare visit: Any visit made to a pharmacy, private practitioner, traditional healer or medical facility to seek care from the reported onset of symptoms with the current illness to MDR-TB treatment initiation. This included directly observed therapy (DOT) visits for those on 1st-line TB treatment prior to MDR-TB treatment initiation; non TB-related visits were excluded.

MDR-TB diagnostic time-point: Defined as either **pre-treatment**, for a presumptive TB case being concurrently evaluated for TB and drug resistance, or as **on 1st line TB treatment**, for a case on a failing 1st-line TB regimen being evaluated for drug susceptibility.

Data Management and Statistical analysis:

Data from the case report forms and cost questionnaire were double entered into a Microsoft SQL database, corrected and analyzed using STATA 12 (StataCorp). Some information on the variables collected was incomplete and only reported data have been analysed. We compared differences between the algorithms and between MDR-TB diagnostic time points. Categorical data were summarized using proportions and compared using the chi-square test. Continuous data were summarized using means and standard deviations or medians and interquartile ranges. Continuous variables were assessed using either the two-sample t-test or Wilcoxon rank sum test depending on the distribution of the variable.

Median as opposed to mean visits and costs are presented as the data were skewed and medians are considered a more representative reflection of the sample. Mean values are presented as supplementary information. We used a quantile regression model to assess the effect of potential confounders such as age, gender, previous TB and HIV status on median visits and costs.

Ethics:

The Health Research Ethics Committee at Stellenbosch University (IRB0005239)(N10/09/308) and Ethics Advisory Group at The International Union Against Tuberculosis and Lung Disease (59/10) approved the study. The City Health Directorate, Western Cape Health Department and National Health Laboratory Service granted permission to use routine health data for which a waiver of informed consent was granted. All study participants provided informed consent for interviews.

RESULTS

Demographic and clinical characteristics:

Of the 226 eligible patients, 153 were interviewed and 73 were excluded (Figure 2). Excluded patients did not differ significantly in gender (p=0.344), age (p=0.561), HIV status (p=0.893), previous TB treatment (p=0.101), or MDR-TB diagnostic time-point (p=0.471) from those included.

Demographic and clinical data are presented in Table 1 for the 89 patients in the LPA and 64 in the Xpert groups. There were no significant differences in sex, age, HIV status, and previous TB treatment between the groups. The majority of patients were diagnosed at the pre-treatment diagnostic time-point in both groups. The median household size was smaller in the LPA than the Xpert group (p=0.001).

Healthcare visits from the start of illness to MDR-TB treatment initiation:

The median number of health visits to MDR-TB treatment initiation was reduced from 20 in the LPA group to 7 in the Xpert group (p<0.001) (Table 2). For those diagnosed at the pre-treatment diagnostic time-point, the median number of visits was reduced from 16 in the LPA group to 6 in the Xpert group (p<0.001). There were no significant differences between the groups for those diagnosed whilst on 1st-line TB treatment (p=0.375).

In the quantile regression model (Table 3), age, gender, HIV status and previous TB were not significantly associated with the number of visits. When adjusting for these potential confounders, there were 12 (95% CI 3 to 21, p=0.009) fewer visits in the Xpert group. Cases diagnosed at the pre-treatment diagnostic time-point had 10 fewer visits (95% CI 4 to 15, p>0.001) in the Xpert group. For those diagnosed whilst on 1st line TB treatment, there was no significant difference in the number of visits between the groups (p=0.624).

The proportion of patients who visited a private practitioner was similar, with 30% in the LPA and 31% in the Xpert group (p=0.905). The proportion hospitalized at some point prior to MDR-

TB treatment initiation was also similar with 19% in both groups (p=0.957). A higher proportion attended a healthcare facility or a community site for DOT relating to their 1st line TB regimen in the LPA group (69%) than in the Xpert group (39%) (p<0.001).

Cost to the patient:

The total median cost to the patient from the start of the illness to MDR-TB treatment initiation was reduced from $68.1 (IQR 32.0 to 142.0) in the LPA group to $38.3 (IQR 14.1 to 79.3) in the Xpert group (p=0.004)(Table 4). Median direct costs were $6.7 (IQR $1.1 to $28.2) in the LPA group and $4.4 (IQR 0.0 to $22.2) in the Xpert group (p=0.321). Median indirect costs were reduced from $40.0 (IQR $20.4 to $105.9) in the LPA group to $22.1 (IQR $11.0 to $54.5) in the Xpert group (p=0.003).

All patients incurred indirect costs, but only 34 patients in the LPA group and 22 in the Xpert group incurred direct medical costs with medians of $22.9 (IQR $17.2 to $28.9) and $22.0 (IQR $15.7 to $26.0) respectively. Direct transport cost were incurred by 66 patients in the LPA group and 41 in the Xpert group with medians of $5.3 (IQR 2.7 to 8.1) and $4.6 (IQR 1.6 to 10.3) respectively.

For those diagnosed at the pre-treatment diagnostic time-point, the total median cost to the patient was reduced from $49.8 (IQR 23.7 to 96.4) in the LPA group to $29.0 (IQR 12.5 to 57.6) in the Xpert group (p=0.004). For those diagnosed whilst on 1st line TB treatment the total median cost to the patient was $167.6 (IQR 105.1 to 273.2) in the LPA group compared to $179.4 (IQR 65.8 to 228.7) in the Xpert group (p=0.531).

In the quantile regression model (Table 3), gender, HIV status and previous TB were not significantly associated with costs. When adjusting for these potential confounders, there was a reduction of $35.4 (95% CI 6.1 to 64.7, p=0.018) in median costs in the Xpert group. Cases diagnosed at the pre-treatment diagnostic time-point had a reduction of $23.5 (95% CI $1.7 to $45.2, p>0.035) in the Xpert group. There was no significant difference in costs between the groups (p=0.583) for those diagnosed whilst on 1st line TB treatment. Costs for those diagnosed on 1st line TB treatment were $102.6 higher (p<0.001) in LPA group and $147.9 higher in the Xpert group compared to those diagnosed pre-treatment in each group.

Change in employment status:

From the start of their illness to being interviewed the proportion unemployed increased from 39% to 73% in the LPA group (p<0.001) and from 53% to 89% in the Xpert group (p<0.001) (Table 5). In the LPA group 36% lost employment after the start of their illness compared to 27% in the Xpert group (p=0.222); 94% in both groups reported this to be directly attributable to having contracted MDR–TB. Both patients who stopped schooling or tertiary education in the LPA group and 6 of the 7 in the Xpert group reported this as attributable to MDR-TB.

Change in individual and household income:

In the LPA group 58% earned an income from employment prior to MDR-TB illness compared to 36% in the Xpert group. Of those earning an income, 67% in the LPA group and 65% in the Xpert group lost income between the start of their illness and MDR-TB treatment initiation (Table 5).

Prior to their illness 20 (22%) patients in the LPA group and 17 (27%) in the Xpert group received money from a social grant, of which 1 in the LPA group and 5 in the Xpert group comprised a temporary or permanent disability grant (Table 5). At the time of the interview an additional 36 (40%) in the LPA group and 14 (22%) in the Xpert group (p=0.016) received temporary disability grants, linked to their illness.

In both groups 97% knew or could estimate their monthly household income with 38% in the LPA group and 27% in the Xpert group losing >10% of monthly household income between the start of their illness and time of the interview (Table 5). Overall there was a 16% decrease in median household income in the LPA group compared to 13% in the Xpert group.

DISCUSSION

This study compared costs incurred by MDR-TB patients in an existing LPA-based diagnostic algorithm to that in a newly introduced Xpert-based algorithm from the reported onset of symptoms to MDR-TB treatment initiation. The number of health- visits (and thus costs) was expected to decrease in the Xpert-based algorithm for two reasons: firstly, Xpert provided a

quicker DST result than LPA (median <1 day compared to 24 days to a result being available in the laboratory(19)), thus fewer patients would be started on 1st line TB treatment whilst awaiting a DST result. Secondly, all presumptive TB cases would be simultaneously screened for TB and drug susceptibility in the Xpert group; in comparison, those at low risk of MDR-TB in the LPA group were only evaluated for drug susceptibility when 1st line TB treatment failed (usually after 2-3 months of treatment). An algorithm where all presumptive cases are tested for drug resistance, irrespective of the test used, will decrease the number of pre-treatment visits by earlier identification of drug resistance for many patients.

The introduction of the Xpert-based algorithm decreased the number of pre-treatment healthcare visits from a median of 20 in the LPA group to 7 in the Xpert group. However, the number of visits remains high, especially for patients diagnosed whilst on 1st-line TB treatment. A large contributor to this was DOT visits whilst awaiting a DST result. Visits to private practitioners (similar in both algorithms) and to health centers not offering TB treatment increased the number of pre-treatment visits as patients often made several visits, were not appropriately tested and had to eventually be referred for MDR-TB tests and or treatment.

There was a significant decrease in median costs for patients in the Xpert ($38.3) compared to the LPA group ($68.1). As direct medical costs were similar in both groups (all related to private sector care as public sector services are free) and travel costs were low, this was largely attributable to indirect costs related to time spent in travel and at the healthcare facility. Other TB costing studies have also found higher indirect than direct costs (17,18).

Improved health system efficiencies with the Xpert-based algorithm can help to further reduce indirect costs. To achieve this, healthcare professionals need to adhere to the testing algorithm and health delivery issues such leaking sputum containers, broken fax machines, and mislaid results need to be minimized to eliminate unnecessary pre-treatment visits.

Other studies have found income loss to be the largest financial burden faced by patients contracting TB(14). We found a high proportion of patients, in both algorithms, who lost income as a result of employment loss due to their illness, highlighting the devastating impact MDR-TB can have on a patient's livelihood, irrespective of the speed at which they are diagnosed. Studies are needed to ascertain if people regain employment, once they have commenced or completed

353 treatment, however with the poor treatment outcomes for MDR-TB (27) this is likely to be low.
354 There was a marked loss of monthly household income in both groups. "Catastrophic" costs (14)
355 were experienced by 38% in the LPA group and 27% in the Xpert group who lost >10% of
356 monthly household income.
357
358 When estimating costs, different approaches may influence the cost estimate. In this study
359 indirect costs for patient's time were calculated for all patients based on a basic municipal
360 workers wage. This may have overestimated indirect costs for those unemployed, although this
361 effect may be counter-balanced, as the study did not cost unpaid work in the household and the
362 cost to the unemployed who lost time that could have been used to seek new employment.
363
364 There are also alternative methods of calculating indirect costs – we have used the traditional
365 human capital method, which assumes a loss equivalent to the production that could have
366 occurred in the time foregone, using hourly wages to value this production(28). Alternative
367 methods, such as the friction cost approach(29) assume some reorganization to minimize
368 disruption (e.g. individuals substituting leisure time for paid or unpaid work). Our approach may
369 therefore overstate indirect costs by not accounting for such flexibility, although it is not possible
370 to quantify the impact of this.
371
372 **Strengths and Limitations:**
373
374 As patients were interviewed 3 to 6 months after the start of MDR-TB treatment, recall bias may
375 have influenced findings. A strength of our study was that was that we were able to triangulate
376 visit data from patient interviews with clinical records which is likely to have reduced reporting
377 bias.
378
379 However, the study had limitations. Firstly, this was an observational study conducted in routine
380 operational conditions. Temporal changes such as the full decentralisation of MDR-TB treatment
381 may have contributed to the findings. Secondly, the patients sampled were not representative of
382 all MDR-TB patients. Untreated patients were not included. To reduce the risk of infection to
383 researchers, only patients who had been on MDR-TB treatment for at least 3 months and had
384 smear-converted were interviewed. Patients who were lost to follow-up, which may have been
385 influenced by the high cost of illness, or had failed to smear convert were not included. Healthier

people were thus more likely to be interviewed, which may have underestimated costs, but this is unlikely to have been different between the two algorithms.

Thirdly, we did not assess coping strategies that patients may have resorted to such as the sale of assets and borrowing. Lastly, we have not assessed visits or costs based on clinic performance as the clinic ranking changed each year and the number of patients was too small. The study included the early phase of Xpert implementation, which may have increased the median number of pre-treatment visits in the Xpert group as staff became familiar with the new algorithm and new practices were entrenched.

Implications of Study Findings:

Given the high loss of employment attributable to their having developed MDR-TB, many of these patients and their households are in need of financial support. There have been international calls by the World Health Organisation and International Labour Office for countries to invest in social protection mechanisms such as income replacement and social support for those affected by illness(30).

Although disability grants (monthly value $129.2) are available to support MDR-TB patients and offer a measure of income replacement, access to these was poor with fewer patients receiving a disability grant at the time of the interview in the Xpert (22%) compared to the LPA group (40%). This may reflect the time it takes to process a grant, with this not yet having taken place for those diagnosed in the Xpert-based algorithm. Expedited access to disability grants is required: the provision of unconditional disability grants could be considered for diseases such as MDR-TB as the means-testing process (undertaken by a doctor) contributes to delay. On a positive note, the low direct medical costs incurred by patients bare testimony to the social protection offered by free public health services in South Africa.

CONCLUSION

Assessing the economic relief to the patient and their household is important in understanding the impact of new molecular TB diagnostics. This study has shown that the introduction of an Xpert-based algorithm brought relief by decreasing the costs incurred by patients, mostly by

reducing the number of visits to treatment initiation. Improved health service efficiencies can help further reduce costs.

The link between TB and poverty is strong (1,31). In our setting, even though MDR-TB diagnosis and treatment are free and easily accessible, the economic impact of MDR-TB was large, with many patients losing employment and individual and household income. It is important for health planners to be cognizant of the fact that irrespective of how quickly treatment is initiated with a rapid MDR-TB test, a high number of patients will be vulnerable to the effects of increased poverty. Efforts need to be made to mitigate this to break the poverty-illness cycle.

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Table 1: Demographic, Socioeconomic and Clinical Characteristics of Study Patients

Variable	LPA Group (n=89)	Xpert Group (n=64)	p-value
Sex, Female (number, %)	44 (49%)	27 (42%)	p=0.375
Mean Age, years SD (Range)	36.8 10.7 (19-70)	35 .3 9.7 (19-63)	p=0.300
HIV-positive (number, %)	57 (64%)	34 (53%)	p=0.175
Previous TB treatment (number, %)	45 (51%)	30 (47%)	p=0.633
MDR-TB diagnostic time-point: Pre-treatment (number, %)	74 (83%)	55 (86%)	p=0.640
Highest Education level attained[1] (number, %) • No education • Primary school education (Grade 1-Grade 7) • Some high school education (Gr 8- Grade 11) • Completed high school education (Grade 12) • Tertiary education	 2 (2%) 29 (33%) 44 (49%) 13 (15%) 1 (1%)	 0 (0%) 15 (24%) 36 (57%) 7 (11%) 5 (8%)	p =0.127
Median number of people in household IQR	3 2-4	4 3-5.5	p=0.001
Median number of dependents IQR	2 1-3	1 0-2.5	p=0.278

[1]*Education level was missing for one patient in the Xpert group.*

Abbreviations: LPA= MDRTBPlus line probe assay; Xpert = Xpert MTB/RIF; SD= Standard Deviation; HIV=Human Immunodeficiency Virus; TB=Tuberculosis; MDR-TB= Multidrug Resistant Tuberculosis; IQR= Interquartile Range

Table 2: Median Number of Healthcare Visits in the LPA and Xpert Groups

	Median	IQR	Min-Max	p-value
LPA Group - all patients (n=89)	20	10-44	2-171	p<0.001
Xpert Group - all patients (n=64)	7	4-23	2-184	
LPA Group – pre-treatment (n=74)	16	7-28	2-164	p<0.001
Xpert Group –pre-treatment (n=55)	6	4-12	2-73	
LPA Group – on 1st line TB treatment (n=15)	77	48-126	25-171	p=0.373
Xpert Group - on 1st line TB treatment (n=9)	51	46-77	19-184	

The table shows unadjusted data. Healthcare visits include all visits to both the public and private health sector. Visits for directly observed therapy (DOT) are included for patients on a 1st line TB regimen, either whilst awaiting drug susceptibility test results or for those who were not evaluated when diagnosed with TB. Only 1.4% of visits in the LPA group and 3.2% in the Xpert group were to the private sector.
Abbreviations: LPA = MDRTBPlus line probe assay; Xpert = Xpert MTB/RIF; TB = Tuberculosis; IQR = Interquartile Range; Min-Max = Minimum – Maximum
Data on mean visits are presented in supplemental information.

567 **Table 3: Quantile Regression Model Outputs for Number of Healthcare Visits and Patient Costs**

568

Variable	Coefficient	Standard Error	p-value	95% Confidence
Adjusted Data for Number of Healthcare Visits – All patients				
Xpert Group	-11.9	4.5	0.009	-20.8 to -3.1
Gender	5.4	4.5	0.224	-3.4 to 14.3
HIV status	-0.9	4.5	0.843	-9.8 to 8.0
Age	-0.1	0.2	0.742	-0.5 to 0.4
Previous TB	-0.4	4.4	0.921	-9.2 to 8.3
Constant	20.8	9.2	0.026	2.5 to 39.1
Adjusted Data for Number of Healthcare Visits – Patients at Pre-treatment Diagnostic Time				
Xpert Group	-9.6	2.7	0.001	-14.9 to -4.2
Gender	2.3	2.7	0.401	-3.1 to 7.6
HIV status	-0.1	2.7	0.979	-5.4 to 5.3
Age	-0.1	0.1	0.524	-0.4 to 0.2
Previous TB	1.8	2.7	0.509	-3.5 to 7.1
Constant	17.2	5.8	0.004	5.6 to 28.7
Adjusted Data for Number of Healthcare Visits – Patients at Treatment Diagnostic Time Point				
Xpert Group	-13.4	26.8	0.624	-69.8 to 43.0
Gender	16.6	24.7	0.510	-35.3 to 68.5
HIV status	15.7	25.4	0.545	-37.7 to 69.2
Age	-0.9	1.1	0.405	-3.3 to 1.4
Previous TB	57.9	35.2	0.117	-16.0 to 131.8
Constant	88.7	42.2	0.050	0.1 to 177.3
Adjusted Patient Cost Data ($) – All patients				
Xpert Group	-35.4	14.8	0.018	-64.7 to -6.1
Gender	9.4	14.7	0.524	-19.7 to 38.5
Previous TB	-15.2	14.6	0.298	-44.0 to 13.6
HIV status	-0.7	15.0	0.962	-30.4 to 28.9
Constant	74.3	16.5	<0.001	41.7 to 107.0
Adjusted Patient Cost Data ($) – Patients at Pre-treatment Diagnostic Time Point				
Xpert Group	-23.5	11.0	0.035	-45.2 to -1.7
Gender	7.3	10.9	0.506	-14.3 to 28.8
Previous TB	1.9	10.8	0865	-19.6 to 23.3
HIV status	-1.7	11.1	0.880	-23.6 to 20.3
Constant	48.8	12.9	<0.001	23.2 to 74.3
Adjusted Patient Cost Data ($)– Patients at Treatment Diagnostic Time Point				
Xpert Group	-55.4	99.1	0.583	-262.8 to 152.1
Gender	48.8	90.3	0.595	-140.3 to 237.9
Previous TB	114.1	130.2	0.392	-158.4 to 386.5
HIV status	3.4	92.7	0.972	-190.7 to 197.4
Constant	121.2	86.8	0.179	-60.5 to 302.9
Adjusted Cost Comparison at the different Diagnostic Time Points in the LPA-based Algorithm				
Pre-treatment	102.6	25.0	<0.001	52.8 to 152.4
Constant	69.2	21.3	0.002	26.8 to 111.6
Adjusted Cost Comparison at the different Diagnostic Time Points in the Xpert-based				
Pre-treatment	147.9	24.3	<0.001	99.3 to 196.5
Constant	14.6	15.5	0.349	-16.4 to 45.6

Table 4: Median Patients Costs in the LPA and Xpert Groups

	n	Median Direct Costs ($) (IQR)				Median Indirect Costs ($) (IQR)				Median Total Cost to Patient (IQR) p-value	
		Transport Costs	Medical Costs	Direct Costs p-value		Cost of Transport Time	Cost of Time in Health Facility	Indirect Costs p-value			
LPA Group – all patients	89	3.4 (0-6.9)	0 (0-18.1)	6.7 (1.1-28.2)	p=0.321	12.3 (6.2-29.6)	23.7 (11.7-64.4)	40.0 (20.4-105.9)	p=0.003	68.1 (32.0-142.0)	p=0.004
Xpert Group – all patients	64	1.5 (0-6.5)	0 (0-16.0)	4.4 (0.0-22.2)		4.6 (2.6-14.3)	13.4 (8.2-39.0)	22.1 (11.0-54.5)		38.3 (14.1-79.3)	
LPA Group – Pre-treatment	74	3.2 (0-6.9)	0 (0-18.1)	6.5 (1.1-25.9)	p=0.345	9.9 (5.8-23.2	19.9 (8.9-46.1)	33.7 (17.5-87.1)	p=0.005	49.8 (23.7-96.4)	p=0.004
Xpert Group – Pre-treatment	55	1.5 (0-6.5)	0 (0-15.7)	4.2 (0.0-20.3)		4.0 (2.5-9.9)	12.1 (7.3-30.3)	17.3 (10.9-46.7)		29.0 (12.5-57.6)	
LPA Group - on 1st line TB treatment	15	4.5 (0-6.2)	0 (0-24.1)	27.5 (0.0-30.0)	p=0.928	54.8 (30.1-91.2)	86.4 (31.9-117.0)	164.7 (76.1-234.5)	p=0.297	167.6 (105.1-273.2)	p= 0.531
Xpert Group - on 1st line TB treatment	9	3.4 (0-21.7)	0 (0-22.9)	4.6 (0.0-44.6)		25.4 (21.6-46.9)	37.0 (19.1-155.6)	61.3 (46.7-202.4)		179.4 (65.8-228.7)	

Costs and time associated with seeking help were calculated from the onset of illness to MDR-TB treatment initiation in South African Rands, adjusted to 2013 values based on the consumer price index, and converted to US$ at a rate of 9.75 (average United Nations Treasury operational rates in 2013). The total cost to the patient is the sum of the direct and indirect costs.

The table shows data for all patients in both groups. However, only 67patients in the LPA group and 45 in the Xpert group incurred direct costs with medians of $20.5 (IQR 5.0 to 30.3) and $12.4 (IQR $3.4 to $30.4) respectively. Direct medical costs were incurred by 34 patients in the LPA group and 22 in the Xpert group with median costs of $22.9 (IQR $17.2 to $28.9) and $22.0 (IQR $15.7 to $26.0) respectively. Direct transport cost were incurred by 66 patients in the LPA group and 41 in the Xpert group with median costs of $5.3 (IQR 2.7 -8.1) and $4.6 (IQR 1.6-10.3) respectively.

Abbreviations: LPA = MDRTBPlus line probe assay; Xpert = Xpert MTB/RIF; IQR = Interquartile Range

Mean costs are presented as supplemental information.

Table 5: A Comparison of Employment Status and Individual and Household Income

	LPA Group (n = 89)	**Xpert Group** (n = 64)	**p-value**
Number unemployed prior to illness (%)	35 (39%)	34 (53%)	p=0.091
Number unemployed at time of interview (%)	65 (73%)	57 (89%)	p=0.015
Median monthly income from salary prior to illness amongst employed ($) (IQR)[1]	228.9 (153.4-330.9)	265.6 (194.7-303.6)	p=0.628
Median loss of monthly income from salary from start of illness to time of interview amongst employed ($) (IQR)	224.4 (144.2-320.5)	251.9 (160.3-303.6)	p=0.719
Of those receiving a grant pre-illness: number receiving money from a disability grant (%)	1 (1%)	5 (8%)	-
Additional number receiving money from a disability grant at time of interview (not including those above) [2]	36 (40%)	14 (22%)	p=0.016
Number receiving money from any grant pre-illness (as % of total)	20 (22%)	17 (27%)	p=0.560
Median monthly grant amount ($) pre-illness (IQR)	32.4 (30.9-80.5)	60.7 (30.4-137.3)	p=0.298
Median monthly additional grant amount at the time of the interview($)[3] (IQR)	123.6 (121.4-125.9)	126.6 (123.1-130.1)	p=0.593
Median monthly household income from all sources prior to illness ($) (IQR)	259.3 (130.5-427.9) *n = 86*	356.6 (130.5-618.2) *n = 62*	p=0.057
Median monthly household income from all sources at time of interview ($) (IQR)	216.8 (123.6-343.5) *n = 86*	308.9 (130.1-471.6) *n = 60*	p=0.043
Number of households losing monthly household income after becoming ill (reported at time of interview) (%)[4]	33 (38%) *n = 86*	17 (27%) *n = 62*	p=0.165

Where data was incomplete or refers to a subset, we specify the denominator as: n = number reported.

All income or loss thereof was recorded in South African Rands, adjusted to 2013 values based on CPI, and converted to US$ at a rate of 9.75 (average United Nations Treasury operational rates in 2013).

[1] *52 patients in the LPA and 23 patients in the Xpert group earned an income from their occupation prior to the start of illness and 52 in the LPA and 22 in the Xpert groups were able to report their income.*

[2] *19 previously employed patients in the LPA group and 4 in the Xpert group received a monthly disability grant of $129.2*

[3] *Additional grants were all temporary disability grants linked to their illness.*

[4] *All households losing income lost >10% of monthly household income.*

Abbreviations: LPA = MDRTBPlus line probe assay; Xpert = Xpert MTB/RIF; IQR = Interquartile Range; MDR-TB = Multidrug Resistant Tuberculosis.

Figure 1: Testing in the LPA and Xpert-based TB Diagnostic Algorithms

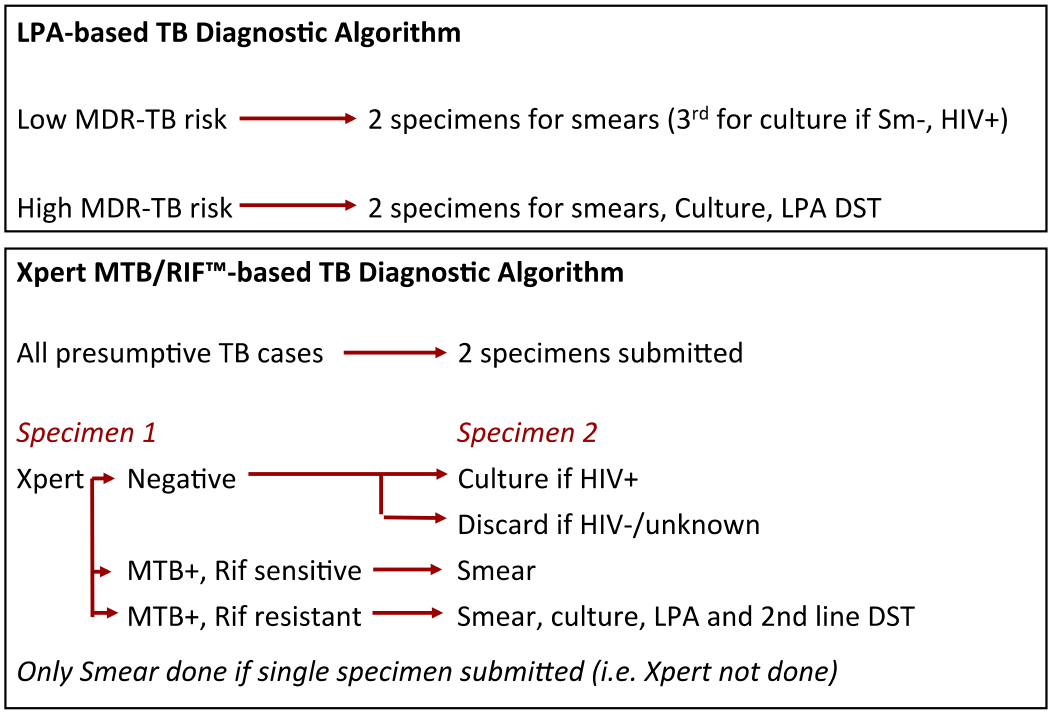

Figure 2: Study Population